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REMARKS

The Advisory Action indicates that claims 54-71 and 123-155 were pending prior to this Supplemental Response, with claims 1-53 and 74-155 being withdrawn from consideration. However, as claims 72 and 73 are neither cancelled or withdrawn from consideration, Applicants respectfully submit that claims 54-73 and 123-155 were pending prior to this Supplemental Response, with claims 1-53 and 74-155 being withdrawn from consideration. New claim 156 has been added. By the present communication, claims 1-53, 56, and 74-155 are cancelled without prejudice, new claims 156 has been added, and claims 54, 58, 69 and 70 are amended as shown in attached Exhibit A to define Applicants' invention with greater particularity. The amendments add no new matter, being fully supported by the Specification and original claims. Accordingly, claims 54, 55, 57-73 and 156 are currently pending and under consideration.

The amendments and remarks contained herein are in addition to those contained in the Response to Office Action filed herein on October 16, 2001 and the Supplemental Response filed herein on July 10, 2002 in which claim 54 was amended, and are further in reply to the Advisory Action mailed herein on October 22, 2002.

Applicants wish to thank Examiner Loeb for thoughtful discussion and comments in an interview with Applicants and Applicants' representative on January 17, 2003. Applicants respectfully request reconsideration of this application in view of that discussion.

The Objection to Figures 12-17

Applicants note the Examiner's concern regarding Figures 12-17 for being partially obscured due to existence of hole punches. Applicants submit as Attachment B a proposed

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drawing correction for Figures 12-17 in which the hole punches do not occur so that any partial obscuring of the Figures does not occur. Applicants will submit formal drawings upon allowance of the claims.

The Rejection under 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 54, 55, 57-71 as allegedly being indefinite under 35 U.S.C. § 112, Second Paragraph. With regard to claim 54, the Examiner asserts that the "nexus" between the recited detectable marker and the rest of the claim is unclear.

By the present communication, Applicants have amended claim 54 to clarify that interaction of the naturally-occurring molecule and the target cell component may cause expression of the detectable marker, which "change in expression" is detected to determine the ability of the naturally occurring molecule to modulate activity of the target cell component. The effect of the naturally occurring molecule on the target cell component activity may be direct or indirect (i.e. resulting from a molecule formed by interaction of the naturally-occurring molecule and the target cell component).

In addition, the Examiner asserts that sufficient antecedent basis for the phrase "the cell component" is lacking in claims 54 and 70. By the present amendment, claims 54 and 70 have been amended to replace the phrase "the cell component" to recite "the target cell component" for which antecedent basis is provided in line 2 of claim 54.

With regard to claim 69, the Examiner asserts that the phrases "the fluorescent dye" and "a visible dye" in line 1 lack sufficient antecedent basis. To clarify that fluorescent dyes and visible dyes are two types of detectable marker, claim 69 has been amended to recite "wherein the detectable marker is a fluorescent dye or a visible dye and detection of the fluorescent dye or the visible dye is carried out by fluorometric or spectrophotometric measurement" thereby providing proper antecedent basis within claim 69 for the terms at issue.

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The Rejection Under 35 U.S.C. § 102 (e)

Applicants respectfully traverse the rejection of claims 54, 55, 58-63, and 67-69 under 35 U.S.C. § 102 (e) as allegedly being anticipated by Thompson et al. (U.S. Patent No. 5,824,485; hereinafter "the '485 patent"). Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (In re Spada, 15 USPQ 2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 2d 1566 (Fed. Cir., 1990). Applicant's invention methods for identifying an a molecule derived from a mixed population gene expression library that modulate the activity of a target cell component, as defined by amended claim 54, distinguish over the disclosure of Thompson by requiring:

"co-encapsulating a naturally-occurring molecule from the library and a cell expressing a target cell component of interest and a detectable marker, in a microenvironment under conditions that allow the naturally-occurring molecule and the target cell component to interact; and

screening the microenvironment to determine the ability of the molecule to modulate activity of the target cell component to produce a change in expression of the detectable marker, wherein the change identifies a molecule that modulates the activity of the target cell component."

Thus, Applicants' presently claimed invention, as defined by amended claim 54, is not the purposeful creation of novel activities or pathways by combinatorial techniques, but rather expression cloning of naturally-occurring molecules, such as DNA derived from a mixture of uncultivated organisms, to produce libraries that contain naturally occurring activities or gene clusters or pathways or genes as found in nature, without manipulation to create a combinatorial library. It can be envisioned that once Applicants have cloned DNA producing such activities or pathways as they occur naturally in organisms in the environment, such molecules could be further manipulated by substituting genes or portions thereof from other species or strains using combinatorial methods.

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Thus, Applicants reiterate that the claimed invention is not directed to a "combinatorial library," but rather recites screening environmental libraries containing sequences that are naturally occurring and which have not been rearranged or recombined in a laboratory setting for the purpose of creating new, combinatorially produced pathways.

By contrast, Applicants respectfully submit that the '485 patent fails to describe each and every element of Applicants' methods for identifying a molecule derived from a mixed population gene expression library that modulates activity of a target cell component, as defined by amended claim 54. Instead, the '485 patent describes *combinatorial* gene expression libraries constructed by stochastic genetic manipulation from genetic material of organisms that are known or are prospective sources of drugs. For example, the '485 patent teaches that individual genes from different species can be concatenated in a way that is predetermined so as to produce a potentially novel, but non-naturally occurring pathway. In addition, the '485 patent teaches cloning genes, at least one of which is a known gene, from several different organisms into a single host cell, with the result being the formation of potentially new pathways. For example, in the '485 patent, a single host cell might contain gene A, which is a known gene, from organism A, gene B from organism B and gene C from organism C, thereby producing a novel metabolic pathway encoded by genes combined from various organisms.

Applicants provide extrinsic evidence in support of the meaning of "combinatorial" as used in the '485 teaching to distinguish from Applicants' teaching and claims directed to naturally occurring DNA encoding molecules that modulate activities of target cell components. Exhibit B is a print out from an internet site which includes a description of Neugenesis' combinatorial biology technology, which creates "combinatorial panels of heavy and light chains of a heteromeric protein and to build libraries of diverse, new, fully assembled proteins. Variants of each subunit gene are generated within the host by Neugenesis' proprietary technology." (<http://www.neugenesis.com/>) Clearly, Applicants' claims are not directed to combinatorial

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approaches to identifying enzyme activities encoded by naturally occurring gene clusters, since Applicants are not manipulating the DNA to generate variants.

Exhibit C is a printout from the internet site of the Koide Group, from University of Pittsburgh (<http://www.pitt.edu/~sparano/group/>). As you will note, this website describes the study of Natural Products as separate and distinct from the study of Combinatorial Libraries. Exhibit D provides a glossary of terms used in Medicinal Chemistry. On page 4, the term combinatorial synthesis is described as "...combining sets of building blocks" e.g., ligating together individual genes of a gene cluster.

Applicants submit that all of this evidence supports Applicants' prior arguments distinguishing Applicants' claimed invention from the combinatorial methods described in the '485 patent. Accordingly, Applicants respectfully submit that Thompson fails to teach each and every element of the claimed invention as would be required to support a rejection under 35 U.S.C. §102(e) and reconsideration and withdrawal of the rejection are respectfully requested.

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In view of the above amendments and remarks, reconsideration and favorable action on claims 54, 55, and 57-73 and new claim 156 are respectfully requested. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Attachments: Exhibits A – D
Corrected Figures 12-17